Εφαρμογές Βιοϋλικών: Αναγεννητική Ιατρική

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Τμήμα Μηχανολόγων Μηχανικών | Ε.Μ.Π.

Χειμερινό Εξάμηνο 2015

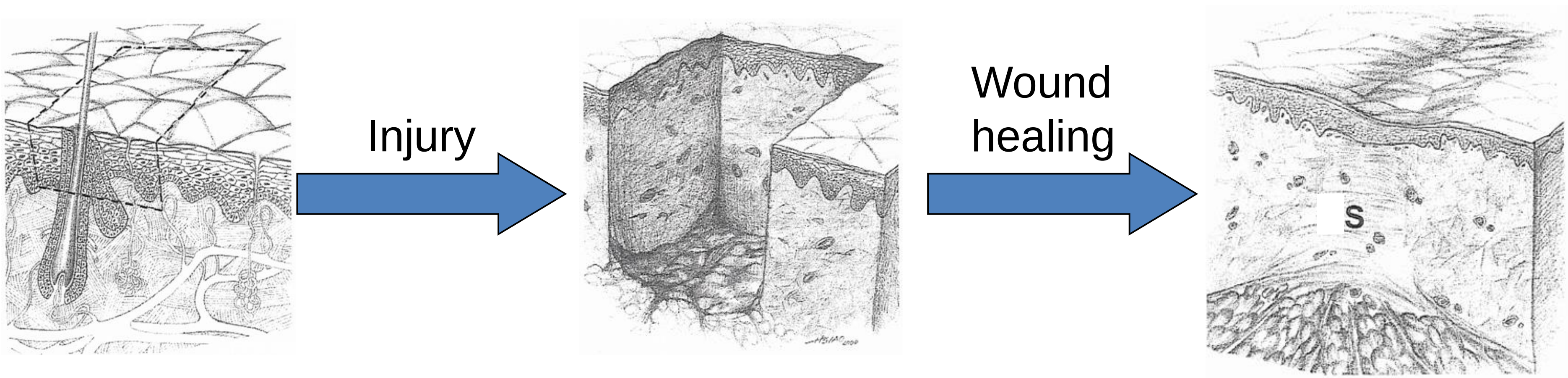
Presentation Outline

- Introduction
  - Clinical Problem
  - Regeneration VS repair
- Biomaterial-induced Regenerative Medicine
- Other Methods for Inducing Regeneration

Introduction

Wound Healing in Adults

- A complex process initiated by injury



Images from Yannas 2001

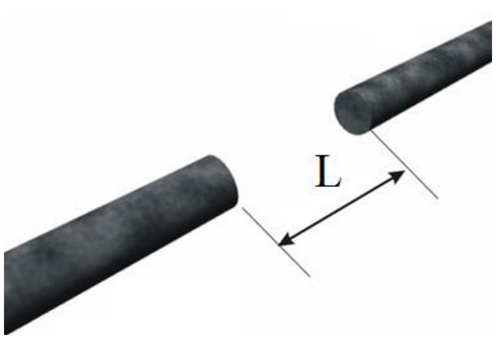
Wound Healing Outcome

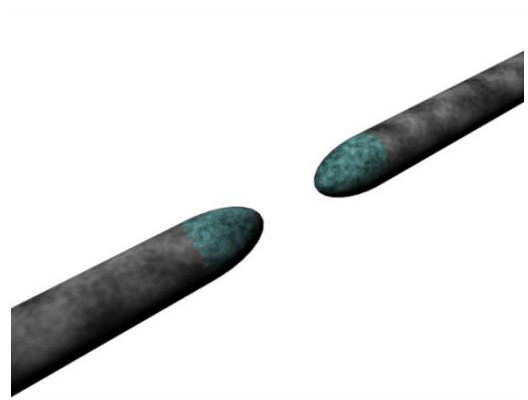
Depends on size and kind of injured tissues

Peripheral nerve injury

Wound healing

Outcome





Regeneration

Normal new tissue

Better outcome

Repair

Abnormal new tissue

The Clinical Need for Regeneration

- Injured organs do not regenerate spontaneously
  - Significant negative impact on the lives of millions

- Current solutions:
  - Transplantations
  - Allografts

- Current solutions suffer from:
  - Limited availability
  - Complications

Regenerative Medicine

- Aim: Develop treatments that can induce regeneration
  - change wound healing process *in vivo*

- Types of treatments
  - Biomaterials
  - Decellularized xenografts
  - Small Molecules
  - Stem Cells

Tissue Engineering VS Regenerative Medicine

- Both attempt to solve same clinical problem
  - Need to replace a damaged organ

- Tissue Engineering approach
  - “Build” organ *in vitro*.. then implant

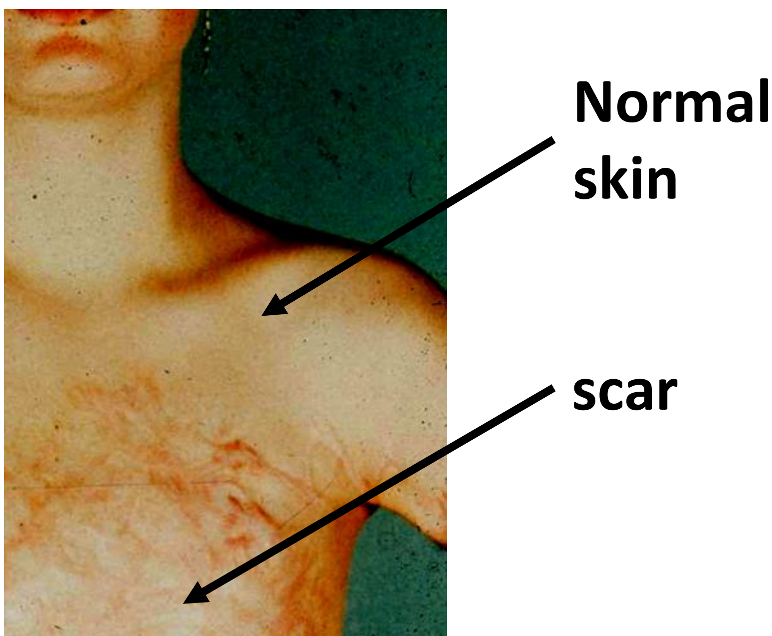
- Regenerative Medicine approach
  - Use treatment that will change wound healing dynamics → body builds organ *de novo* itself

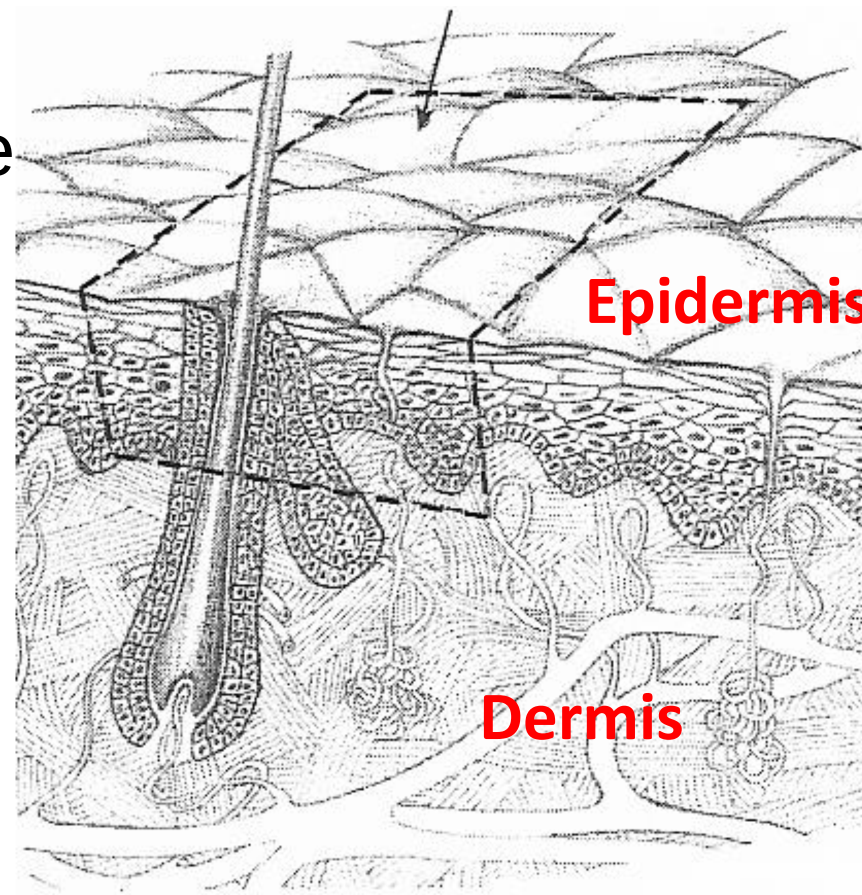
Inducing Regeneration Using Biomaterials

Case Study 1: Skin Regeneration

- Medical Problem: Severe (full thickness) wounds do not regenerate spontaneously

- After severe burn, extensive scars form





Skin Morphology (Yannas 2001)

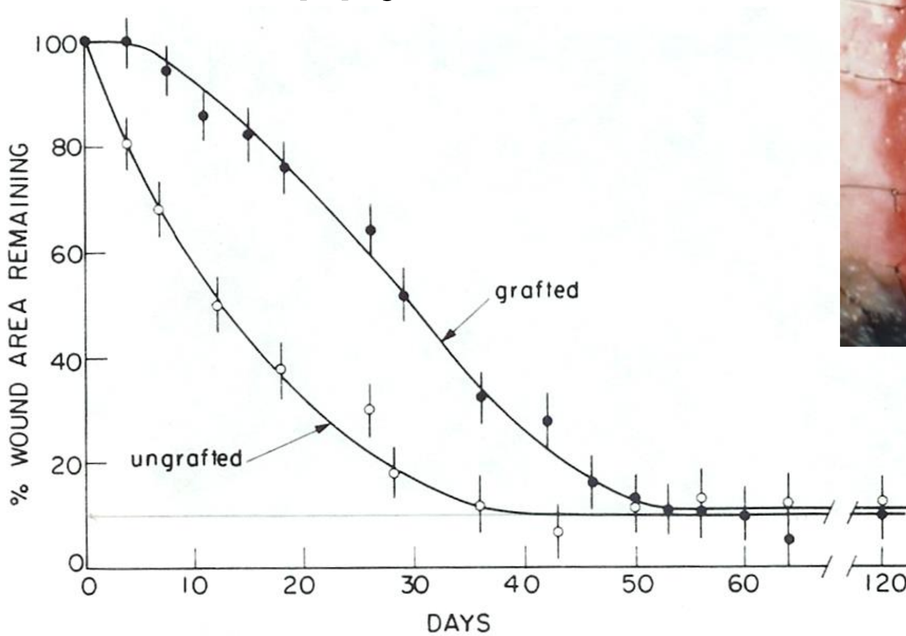
Case Study 1: Skin Regeneration

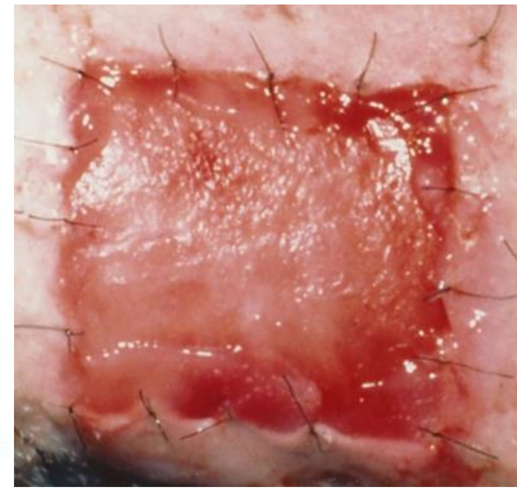
- In the beginning (circa 1975) MDs in Shriner's hospital (Boston) were looking for grafts that can quickly close large skin wounds
  - Prevent bacteria infection in open wounds

- A team was formed between MDs (Shriner's hospital) and engineers (MIT) to test various polymer-based grafts
  - Mostly sheets made of collagen

Case Study 1: Skin Regeneration

- Results showed that some collagen materials <u>delayed</u> wound closure…
  - MDs were not happy at all…





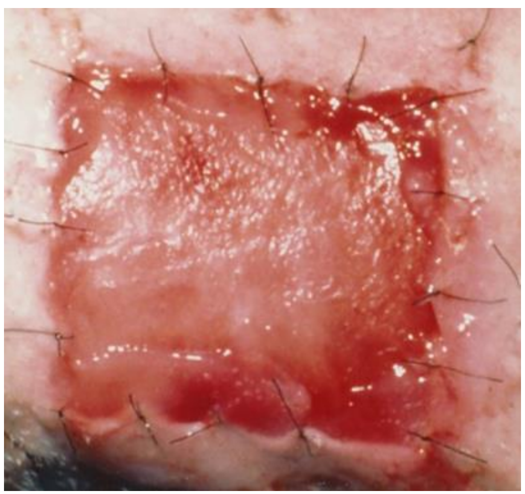
Yannas et al. 1981

- It turned out that the tissue synthesized by these materials consisted of <u>normal dermis</u>

Case Study 1: Skin Regeneration

- <u>Some</u> collagen sheets could induce regeneration
  - The ones that delay wound closure

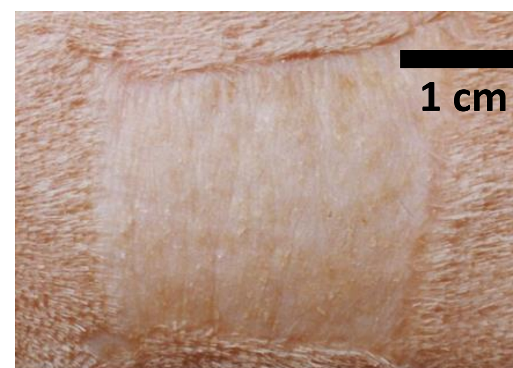
Wound creation | **Wound grafting** | **Wound healing outcome**



"Inactive" biomaterial

Contraction and scar formation

"Active" biomaterial



New dermis formed

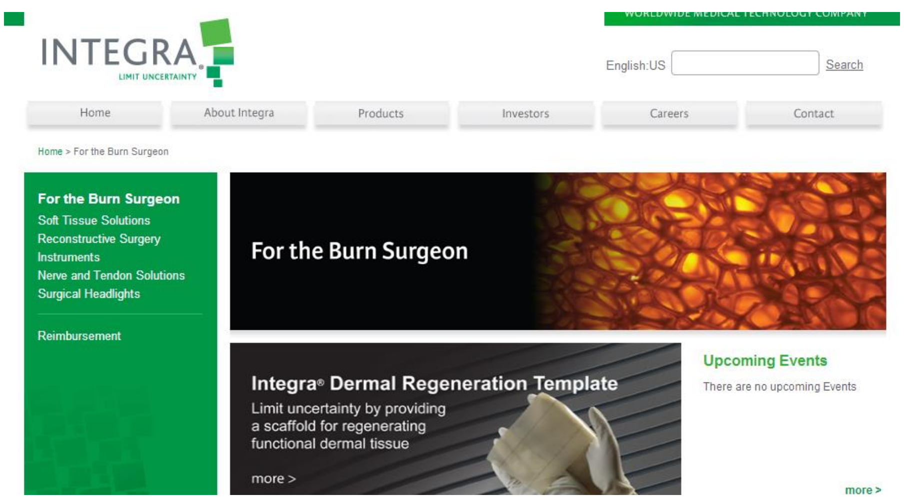
Animal model of dermis regeneration

Orgill, 1983. Courtesy of I.V. Yannas

Case Study 1: Skin Regeneration

- Based on IP of this work, Integra Life Sciences Corp was found
- The product (DRT) is used world-wide by burn and plastic surgeons

CS in the hands of a surgeon
(Integra Life sciences)



United States Patent [19] — **Yannas et al.**

[11] **Patent Number: 4,947,840**
[45] **Date of Patent: Aug. 14, 1990**

[54] **BIODEGRADABLE TEMPLATES FOR THE REGENERATION OF TISSUES**

[75] Inventors: **Ioannis V. Yannas**, Newton; **Elaine Lee**, Medford; **Ariel Ferdman**, Cambridge, all of Mass.

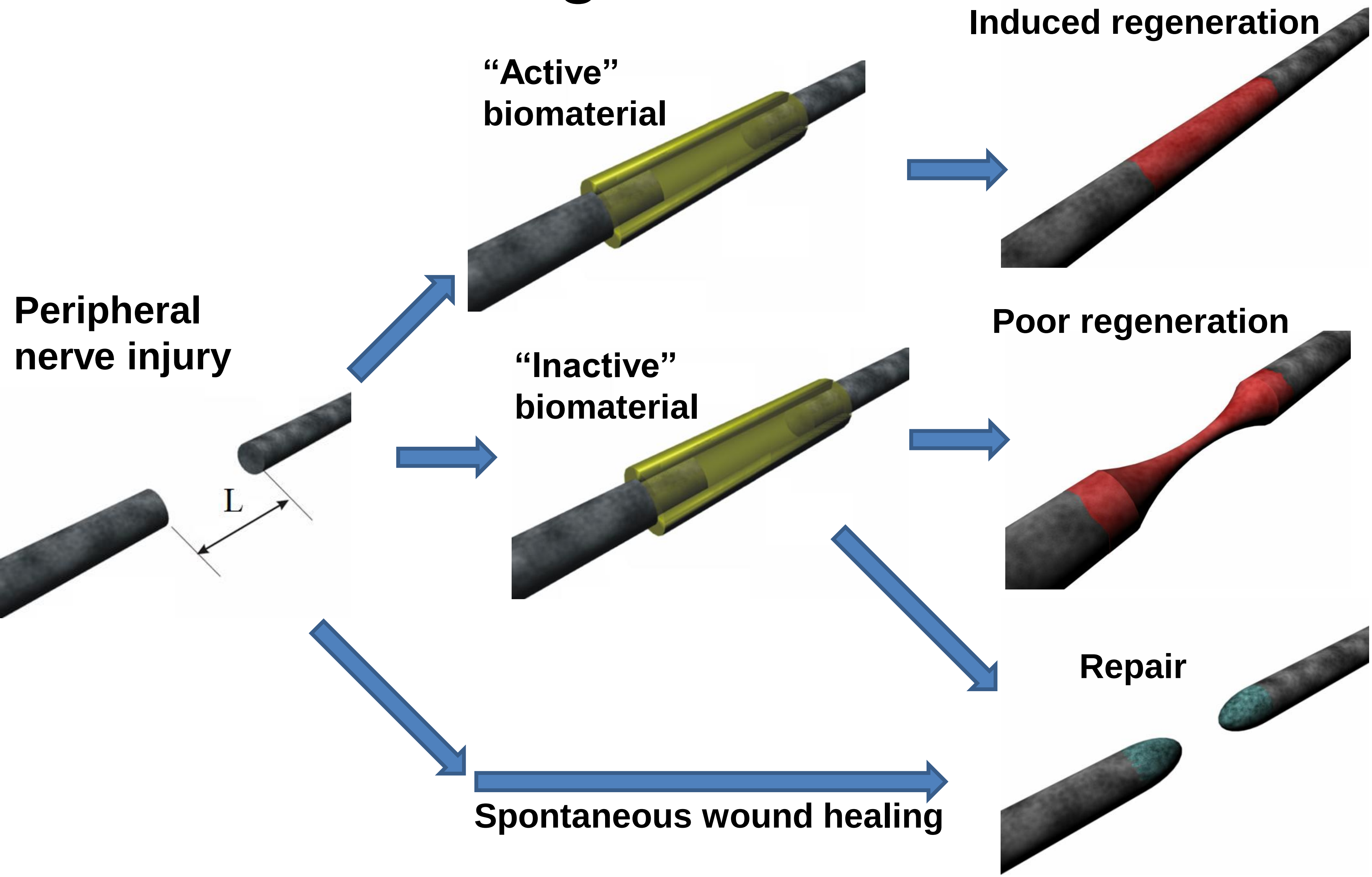
[73] Assignee: **Massachusetts Institute of Technology**, Cambridge, Mass.

4,572,906	2/1986	Sparkes et al.	514/21
4,642,118	2/1987	Kuroyanagi et al.	623/15
4,659,572	4/1987	Murray	514/774
4,767,619	8/1988	Murray	514/774
4,784,653	11/1988	Bolton et al.	604/307
4,841,962	6/1989	Berg et al.	128/156

OTHER PUBLICATIONS

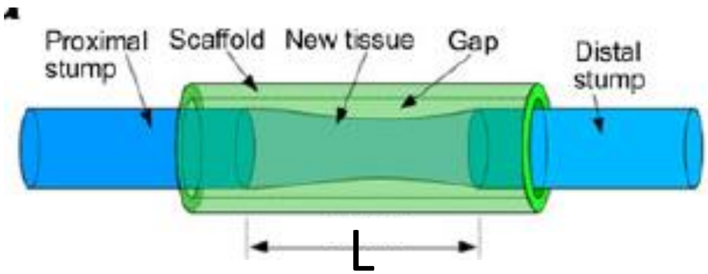
H. F. Fischmeister. Proceedings Int. Symp. RILEM-

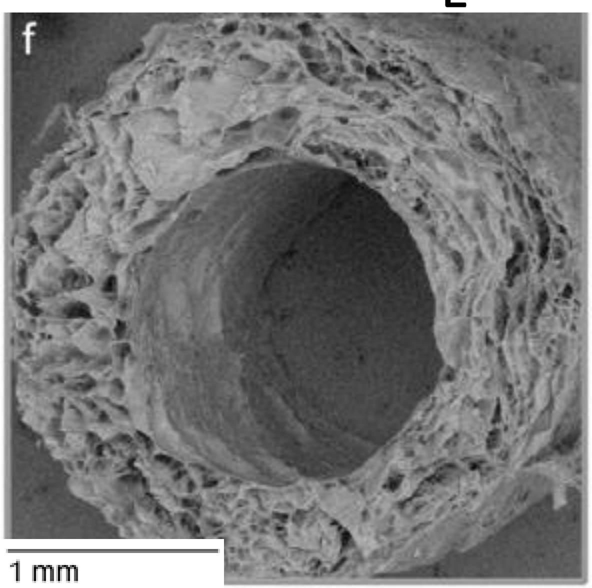
Case Study 2: Peripheral Nerve Regeneration



Case Study 2: Peripheral Nerve Regeneration

- Utilize collagen conduits to connect the two stumps of a transected nerve and induce regeneration
  - Commercially product (Neuragen) available to neurosurgeons





Miu 2009

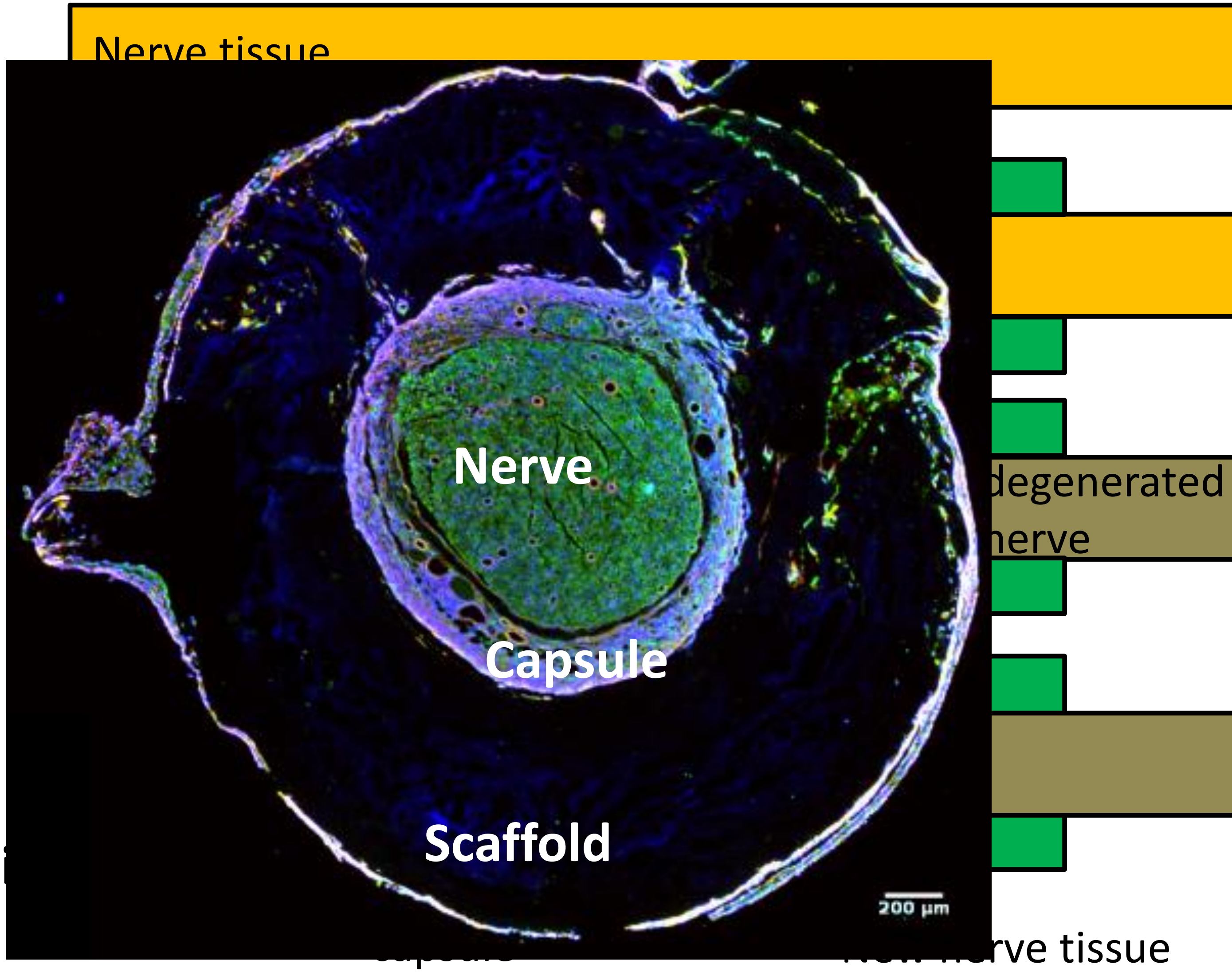
Peripheral Nerve Wound Healing in the Presence of Scaffolds

Healthy PN

Transection & Tubulation

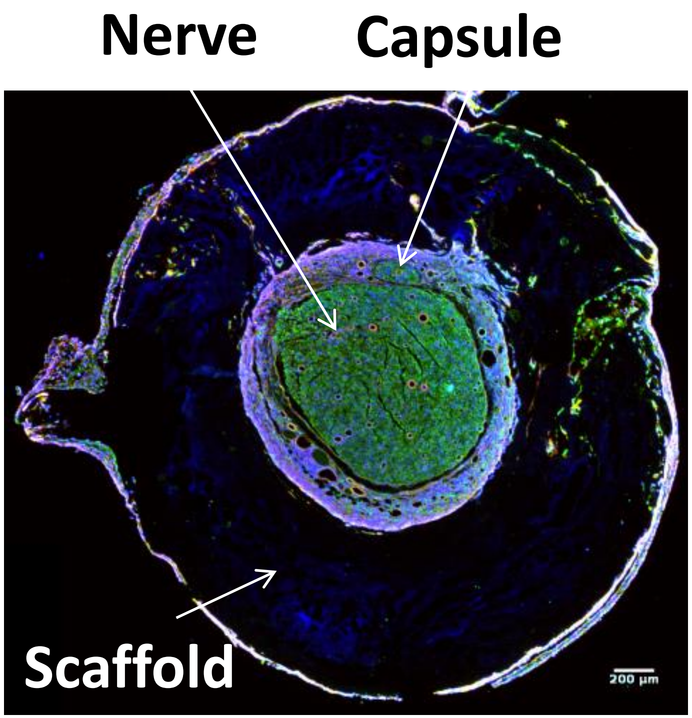
Fibrin clot

Nerve Tissue Synthesis & Capsule Synthesi

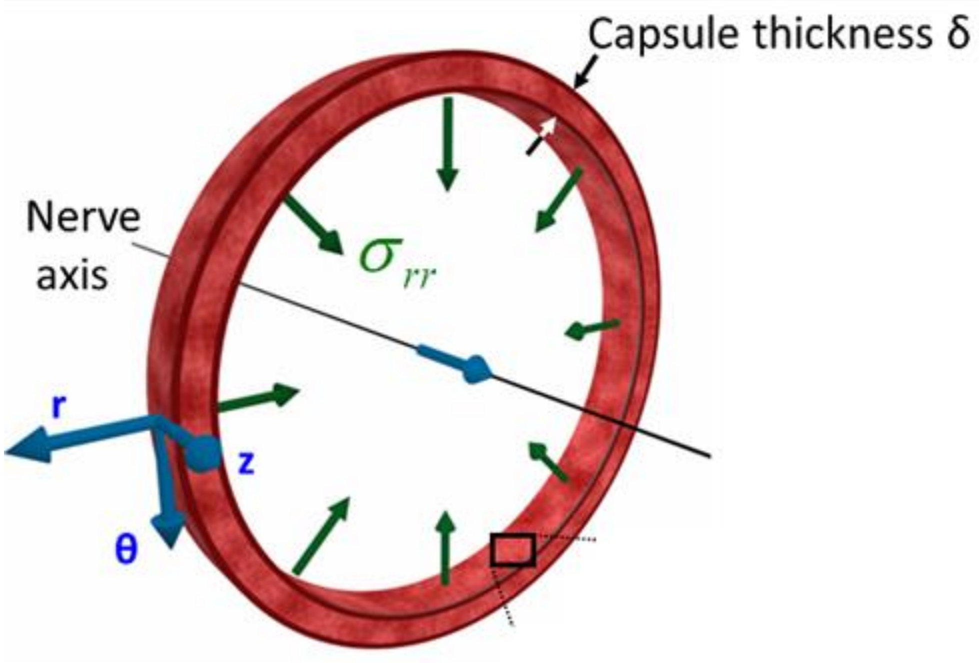


Key Observations: Using Collagen Scaffolds to Induce Regeneration

- "Capsule" of contractile cells surrounds new nerve tissue



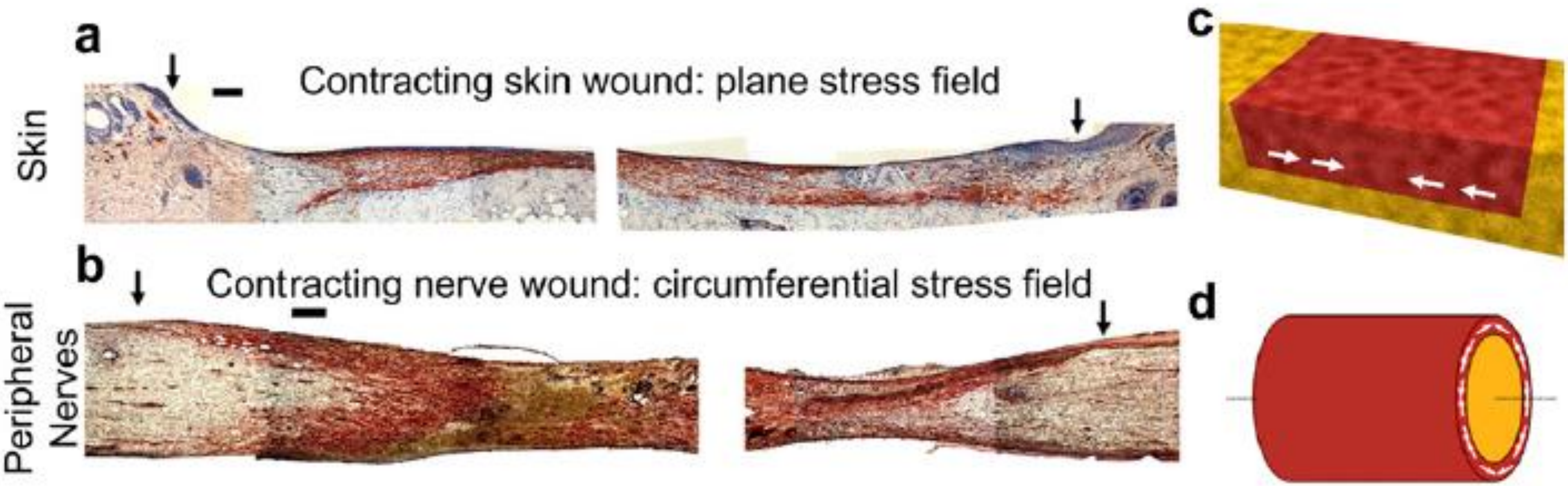
Nerve Cross Section



Force schematic

Key Observations: Using Collagen Scaffolds to Induce Regeneration

- Wound contraction is mediated by contractile cells (myofibroblasts) that form macroscopic capsules and apply forces



Myofibroblast staining in skin and PN wound healing (Soller et al. 2012)

MIT News

ON CAMPUS AND AROUND THE WORLD

Professor Ioannis V. Yannas

Photo: John Freidah

Ioannis Yannas to be inducted into the National Inventors Hall of Fame

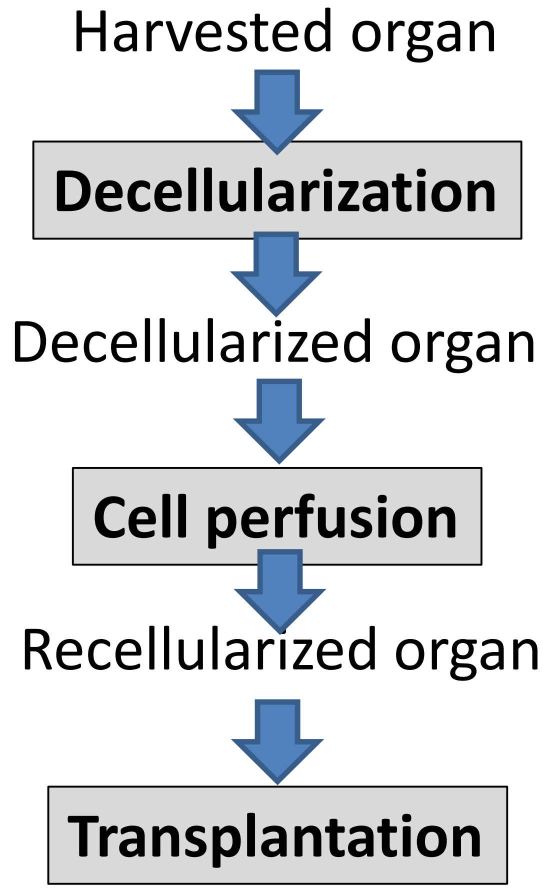
MIT professor of polymer science and engineering recognized for inventing "artificial skin."

Other Methods for Inducing Regeneration

Decellularized Xenografts

- Challenge: Limited offer of human transplant donors

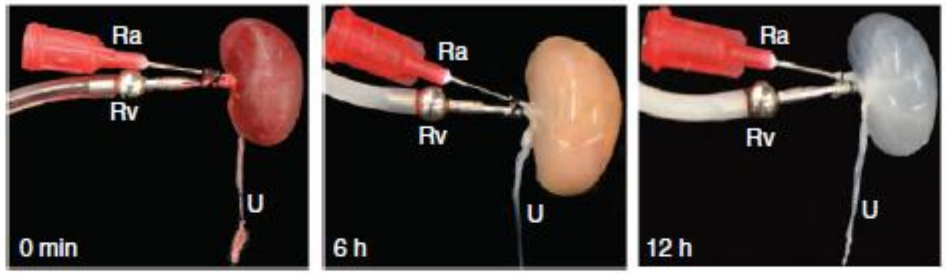
- Solution approach:
  1. Use organs harvested from animals.
  2. Remove immunogenic animal cells
  3. Fill with human cells
  4. Transplant into human patient

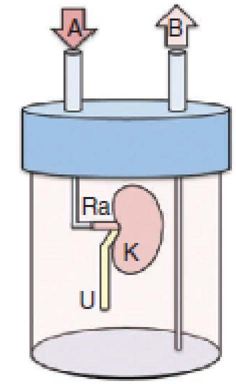


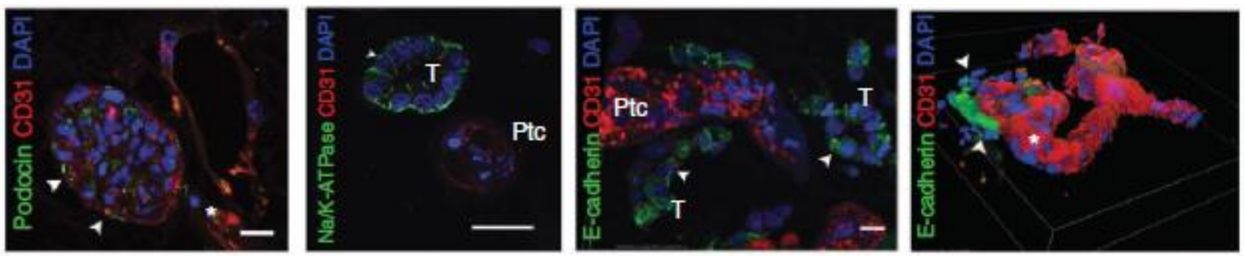
- Decellularized organ can be thought of as a very complex biomaterial

Decellularized Xenografts

- Examples:







TECHNICAL REPORTS

nature medicine

Regeneration and experimental orthotopic transplantation of a bioengineered kidney

Jeremy J Song[1,2], Jacques P Guyette[1,2], Sarah E Gilpin[1,2], Gabriel Gonzalez[1,2], Joseph P Vacanti[1–3] & Harald C Ott[1,2,4]

TECHNICAL REPORTS

nature medicine

Organ reengineering through development of a transplantable recellularized liver graft using decellularized liver matrix

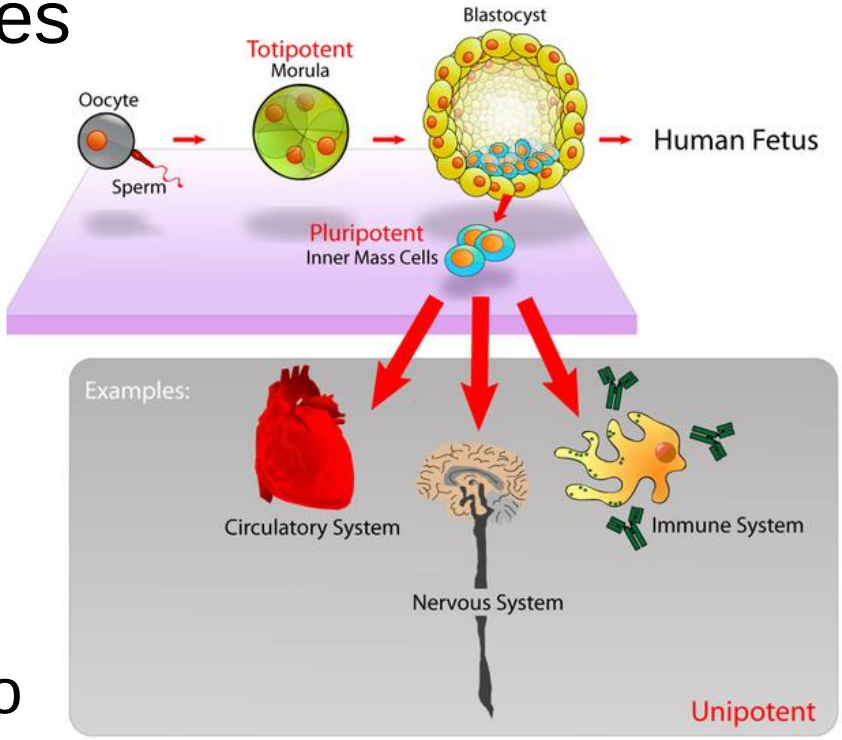
Basak E Uygun[1], Alejandro Soto-Gutierrez[1,6], Hiroshi Yagi[1,6], Maria-Louisa Izamis[1], Maria A Guzzardi[1,2], Carley Shulman[1], Jack Milwid[1], Naoya Kobayashi[3], Arno Tilles[1], Francois Berthiaume[1,4], Martin Hertl[5], Yaakov Nahmias[1,6], Martin L Yarmush[1,4] & Korkut Uygun[1]

Stem Cells

- Potency: the ability of a cell to differentiate into other cell types

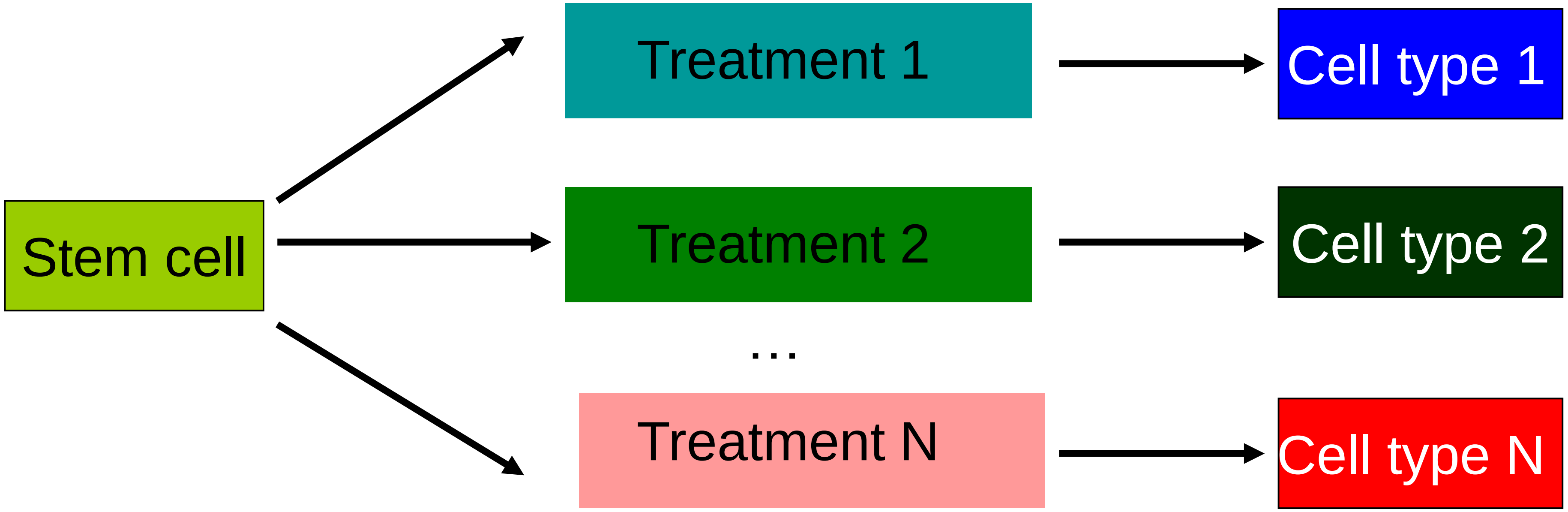
- Stem cells: can proliferate or differentiate into a more “specialized” cell type

- Kinds:
  - Totipotent
  - Pluripotent (can differentiate into any one of 3 germ layers)
    - E.g. Embryonic stem cells
  - Progenitors (multi-potent)
    - E.g. neural stem cells



Stem Cells in Regenerative medicine

- Application:
  - Isolate and amplify stem cells
  - Guide their differentiation (using biomaterials, cytokines, drugs) into cells of the injured organ



- Lots of potential.. No clinical applications yet

Stem Cells in Regenerative medicine

- Various implementations
  - SC differentiation *in vitro* → seed in scaffold → implant
  - Seed SC in scaffold → implant → SC differentiate *in vivo*

- Challenges
  - Isolating stem cells is hard and ethically questionable
  - Control stem cell differentiation is hard and protocols are not known yet

Biomaterials 34 (2013) 5995–6007

Contents lists available at SciVerse ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

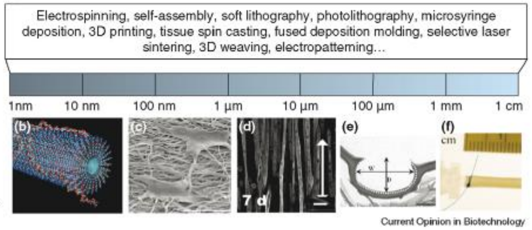
3D matrix microenvironment for targeted differentiation of embryonic stem cells into neural and glial lineages

Chandrasekhar R. Kothapalli[a,*], Roger D. Kamm[b,c]

Polymers to direct cell fate by controlling the microenvironment

R Warren Sands and David J Mooney

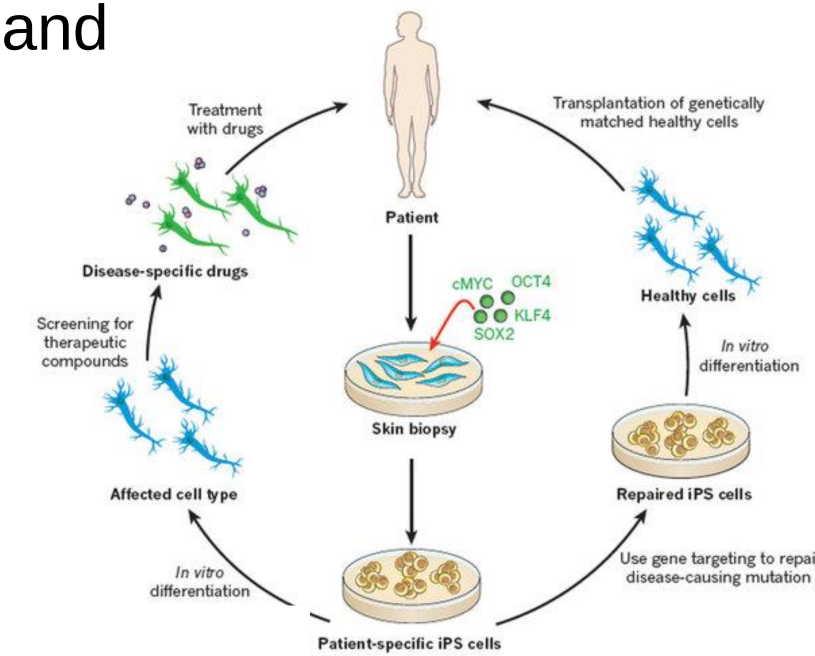
Enhanced understanding of the signals within the microenvironment that regulate cell fate has led to the development of increasingly sophisticated polymeric biomaterials for tissue engineering and regenerative medicine applications. This advancement is exemplified by biomaterials with precisely controlled scaffold architecture that regulate the spatio-temporal release of growth factors and morphogens, and respond dynamically to microenvironmental cues. Further understanding of the biology, qualitatively and quantitatively, of cells within their microenvironments and at the tissue–material interface will expand the design space of future biomaterials.



Current Opinion in Biotechnology 2007, 18:448–453

Induced Pluripotent Stem Cells (iPS)

- Isolating pluripotent SC is hard & ethically questionable
- Induced Pluripotent Stem Cells (iPS)
  - Re-program differentiated cells and convert them to pluripotent SC
  - Provide PS without the need to work with embryonic SC
  - Implemented by inducing specific transcription factors
  - Potentially tumourigenic!



Promise of iPS (*Nature*)

ARTICLE

Received 29 Aug 2013 | Accepted 5 Dec 2013 | Published 28 Jan 2014 DOI: 10.1038/ncomms4071

Generation of folliculogenic human epithelial stem cells from induced pluripotent stem cells

Ruifeng Yang[1], Ying Zheng[2], Michelle Burrows[2], Shujing Liu[1], Zhi Wei[3], Arben Nace[2], Wei Guo[4], Suresh Kumar[1], George Cotsarelis[2] & Xiaowei Xu[1]

Summary

- Injured organs in mammals don't regenerate spontaneously
- Regenerative medicine: treatments that change wound healing in ways that induce regeneration
- Porous collagen scaffolds can induce regeneration in significantly-injured skin and peripheral nerves
  - Outcome depends on scaffold properties
  - Regenerative ability has been attributed to reduced levels of stress in the wound
- Intense research seeks ways to induce regeneration in more organs: new biomaterials, stem cells and iPS, Decellularized Xenografts